IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(s):	Eckart Matthes et al.	CONF. NO.:	
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MAIL STOP AMENDMENT
Commissioner for Patents
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DECLARATION OF ECKART MATTHES

1. My name is Eckart Matthes. I am a citizen of Germany residing at Altlandsberger Chaussee 76, 15345 Eggersdorf.

2. My educational background is in the field of medicine. I obtained the degree(s) of Dr med. and Privatdozent (PD)from Humboldt- Universität, Berlin.

3. I am the head of the department for RNA Chemistry at the Max-Delbrück-Centrum für Molekulare Medizin (MDC), Berlin. Since the beginning of my career in the Department of Prof. Langen at the Institute of Biochemistry of the Academy of Sciences, Berlin (after finishing the study of medicine) I have been concerned with the investigation of nucleoside analogues with the aim of finding new cytostatic agents. Nucleosides as cytostatic and antiviral agents were the topic of my dissertation and

habilitation. After reunification of Germany I become head of a department at the MDC. Furthermore I give lectures on antiviral and cytostatic therapy for students of medicine at the Humboldt-Universität, Berlin.

4. The department for RNA Chemistry at the Max-Delbrück-Centrum für Molekulare Medizin (MDC), Berlin is concerned with two reseach topics: oligonucleotides (ODN) and nucleosides both which were designed, synthesized and investigated in our lab. In the last years my department have developed oligo-nucleotides to inhibit specific cellular function e.g. angiotensinogen, multi-drug-resistance and human telomerase.

5. The telomerase is considered as a cancer target. We designed so called chimeric ODN, which are characterized by different modifications at the 5´-end and the 3´- end to reach two targets of the telomerase, a special protein motif as well as the telomerase RNA which together results in a very strong inhibition of the enzyme (subnanomolar range). These chimeric ODN created for the telomerase are unique. There is no other example for an oligonucleotide binding with one part to the protein and with another part to RNA.

6. The enclosed paper (Nucleic Acids Res. 1999, 27: 1152-1158) describes our finding that phosphorothioate-modified oligonucleotides are competitive inhibitors at the primer binding site of the telomerase protein. We could identify the binding site which is in the nearest neighborhood to the RNA template. Only this finding opens the possibility of linking two ODNs with different targets. An additional paper enclosed

describes the proposed chimeric ODN Oligonucleotides 2005, 268: 255-268)

7. The second topic of our group is the design, synthesis and investigation of nucleoside analogues as inhibitors of viral infections. In the nineteen eighties we discovered the extremely strong inhibition of HIV reverse transcriptase by 3´-fluorothymidine triphosphate and 2´,3´-didehydro-2´,3´-dideoxythymidine triphosphate. Among the nucleosides we synthesized, 3´-fluoro-5-chlorodeoxyuridine and 3´-fluorodeoxyguanosine were potent inhibitors of human immunodeficieny virus- and hepatitis B virus (HBV)-replication, respectively (patent application). For these results I was awarded with the Rudolf-Virchow-Preis. In the nineteen nineties we found that L-thymidine triphosphate is as a strong and very selective inhibitor of HBV DNA polymerase. Now we have developed novel N^4-Hydroxy-L-cytidine analogues as strong inhibitors of HBV replication (patent application).

8.I have carefully studied the specification and claims in the US patent application USSN 09/817,387, and would like to make the following declaration.

9. The Examining division states that claims 1-2, 5, 7, 9-11, 17-20 and 22 are unpatentable over Uhlmann et al. in view of Norton et al. (1996) and Mata et al. arguing that it would have been obvious to combine the teachings of the above-cited references in the design of the present invention and one of ordinary skill in the art would have been motivated to make the oligomers of the present invention wherein n is at least 10 and not more than 20, and p is at least 3 and not more than 17 and to comprise a terminal amino group.

10. This statement has no proper scientific basis.

11. Uhlmann et al. discloses a method for fully automated synthesis of PNA/DNA chimeras. Uhlmann et al. does not teach wherein n is at least 10 and not more than 20, and p is at least 3 and not more than 17.

12. Norton et al. reports the inhibition of telomerase activity by PNAs. In this document the efficacy of PNAs and PS oligiomeres are compared. Results demonstrate higher affinity and specificity of PNAs.

13. Mata et al. describes growth inhibitory effects of an hexameric phosphothioate oligonucleotide (PS-ODN) on humans Burkitt´s lymphoma cells. Mata et al. does not teach the use of PNAs.

14. None of the references teach the formulas used in present invention, wherein n is at least 10 and not more than 20, and p is at least 3 and not more than 17 wherein this oligonucleotide structure comprises a terminal amino group. Further, in none of the documents is the use of the chimeric ODNs, as described in present invention, taught or suggested.

15. Telomerase is a reverse transcriptase synthesizing DNA at the end of chromosomes. This enzyme consists of a protein with the catalytic DNA synthesizing activity and a tightly bond endogenous RNA which carries the template function for the sequence of bases incorporated by the enzyme into the DNA. The telomer DNA sequence is simple and consists of thousands of 5´-

TTAGGG-3´ repeats. The corresponding sequence of the RNA template is 3´-AAUCCC-5´.

16. Therefore oligonucleotides with the sequence TTAGGG carrying all possible chemical modifications can be synthesized, which bind to the RNA template of telomerase thus preventing its template function.

17. All the references cited (Norton, Mata, Uhlmann) used antisense ODN in this usual way to inhibit the telomerase. Between a series of chemical modifications of the applied ODN were also phosphorothioate-modified ODN (PS-ODN). Norton et al. and Matthes et al. (Nature Biotechnol. 1996, 14: 615-618; and Nucleic Acids Res. 1999, 27: 1152-1158) have found that PS-ODN inhibit the telomerase in a sequence unspecific manner. This is not unusual because PS-ODN binds sequence unspecificly to a number of proteins (see first section of the discussion in our paper in Oligonucleotides 2005,15, 255-268, p.263). However, nothing was known about the protein sites which could be able to bind PS-ODN in an unspecific manner.

18. The core point of present invention is the discovery that PS-ODN binds to a protein motif called the primer binding site which normally binds the DNA primer and the demonstration of a competitive interaction of PS ODN with the normal primer to this motif (Nucleic Acids Res. 1999, 27: 1152-1158, p. 1155). Only after this discovery that the binding sites for both the RNA-sequence-specific antisense ODN and the sequence unspecific PS-ODN are in the neighborhood of each other would the possibility of creating chimeric ODN covering both sites ever come to the mind of an experimenter. None of the cited references have

disclosed, proposed or synthesized such chimeric ODN because it is not obvious without our findings to propose and to synthesize such novel telomerase tailor-made chimeric ODN. For this reason it would not have been obvious to combine the cited documents.

19. Uhlmann et al. does not teach oligonucleotide structures comprising a terminal amino group. The examiner states that the terminal secondary amino group in the compounds of Uhlmann et al. can readily be converted to a primary group. But none of the cited references discloses such a step nor do they indicate the importance of such cleavage to a primary amine.

20. Moreover it is easily cognizable from the paper (Oligonucleotides) by the inventors of present patent application that they have cooperated with Dr. Uhlmann (one of the best ODN chemists of the world) and that he was enthusiastic about the idea to hit two targets with one ODN. This shows that not even the editor of one of the cited references was motivated to come to the present invention. This is evidence that the teaching of present invention was not obvious and that, instead, the finding of the invention was completely unexpected.

21. In light of my explanation of what was known to those skilled in the art, the description of the method in the specification of USSN 09/817,387 was not disclosed in the art at the time the invention was made and the references cited do not, alone or in combination, provide sufficient guidance to lead an experimenter to the invention claimed in the instant application.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information

and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

E Matthes — October 9, 2004

Declarant — Date